9

Drug Concentration and Clinical Response

The response of an enzyme, an animal, or a human patient to a drug depends on the dose we give. There is a dose, even of the most potent chemical, that will not elicit a response. A larger dose will produce an effect that we can see or measure, and the intensity will probably increase as we increase the dose. At relatively large doses we may see new and unwanted effects added to the original effect; ultimately, we find a dose large enough to kill or destroy the test system.

The relationship between dose and response is the cornerstone of modern drug therapy. When a patient fails to respond to a dosage regimen, we consider the need for a larger, more effective dose. When a patient manifests undesirable or toxic effects in response to a dosage regimen, we consider the need for a smaller, safer dose. This method for optimization of drug therapy, based on empirical dose adjustment, sometimes succeeds, but is costly and time consuming.

The principal shortcoming of empirical dose adjustments can be found in the dose-response relationship itself. This relationship can be rigorously developed in an individual, but it will not apply to all individuals in a population. Stated another way, the same dose of a drug will produce a different intensity of effect in different individuals. Figure 9–1 shows the distribution of responses to a 0.02 mg/kg intramuscular dose of atropine. The average patient responds with an increase in heart rate of about 20 beats/min, but some patients show no change over resting heart rate, whereas others have an exaggerated response, up to 60 beats/min.[1]

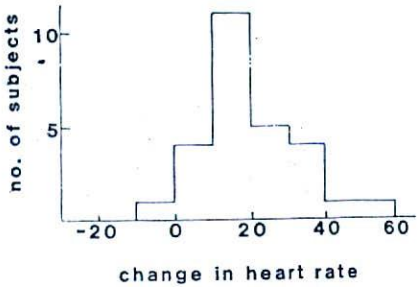

Fig. 9–1. Effect of intramuscular atropine sulfate (0.02 mg/kg) on heart rate (beats/min) in 27 subjects. (Data from Smith, S.E., and Rawlins, M.D.[1])

There are two reasons why a single dose-response relationship does not apply to the population: one reason is called *pharmacodynamic variability* and the other is termed *pharmacokinetic variability*. Pharmacodynamic variability simply means that some individuals are more sensitive or more resistant to the effects of the drug than other individuals. Pharmacokinetic variability means that the same dose of a drug produces different concentrations at the sites of pharmacologic effect in different individuals because of interpatient variability in drug absorption, distribution, excretion, and metabolism.

There is now considerable evidence, from both animal and human studies, that response is better correlated with drug concentrations in blood or plasma than with the administered dose. A classical example is found in the work of Kato and coworkers.[2] The same intraperitoneal dose (110 mg/kg) of zoxazolamine, a muscle relaxant, given to 178 female rats produced a loss of righting reflex that lasted anywhere from 100 to 800 min (Fig. 9–2). Remarkably, the drug concentration in serum

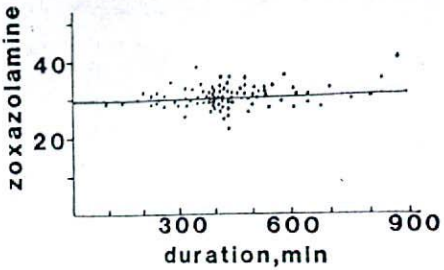

Fig. 9–2. Individual differences in zoxazolamine concentration in serum (μg/ml) on recovery from paralysis after a 110 mg/kg intraperitoneal dose to female rats. (Data from Kato, R., Takanaka, A., and Onoda, K.[2])

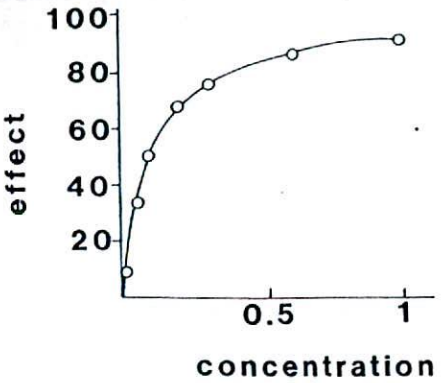

Fig. 9–3. Typical drug concentration-effect relationship resulting from the reversible interaction of drug and receptor. Effect is expressed as percent of maximum response.

at the end of paralysis was about the same in all rats irrespective of the duration of effect. Similar results were found with respect to the duration of narcosis following pentobarbital administration and the serum concentrations of pentobarbital upon recovery.[2]

Remarkable sex differences in response to drugs are well known in the rat. The same dose of hexobarbital produces 19 min of sleep in the male rat but 109 min in the female; however, the brain levels of hexobarbital upon recovery are almost identical in both male and female rats, about 53 μg/g.[3] Sex differences in the mouse are less common. Both male and female mice respond to a 100 mg/kg dose of hexobarbital with a duration of sleep of about 45 min. Despite these substantial species differences, brain levels of hexobarbital upon recovery in both male and female mice are the same as those found in rats.[3] These studies demonstrate the importance of drug concentration in determining drug effect. The relationship between drug concentration and response and the prevalence of pharmacokinetic variability form the cornerstone of clinical pharmacokinetics.

CONCENTRATION-RESPONSE RELATIONSHIPS

Quantitative relationships between drug concentration and response are based on a model for drug response. One model, which is both simple and useful, assumes that a drug interacts reversibly with a receptor in the body; the resultant effect of this interaction is proportional to the number of receptors occupied. The following reaction scheme applies:

$$\text{Drug [D]} + \text{Receptor [R]} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{[DR]} \rightarrow \text{Effect} \qquad (9\text{–}1)$$

This reaction sequence is analogous to the interaction of a substrate with an enzyme; it leads to the following relationship between effect and drug concentration:

$$\text{Effect} = \frac{\text{Maximum Effect [D]}}{K_D + [D]} \qquad (9\text{–}2)$$

where K_D is the dissociation constant for the drug-receptor complex and [D] is drug concentration. There is no effect when [D] = 0; the effect is half-maximum when [D] = K_D (i.e., when half the receptors are occupied); as [D] increases above K_D, the maximum effect is approached asymptomatically. A more familiar form of Eq. 9–2 is:

$$E = \frac{E_{max}\, C}{EC_{50} + C} \qquad (9\text{–}2a)$$

where EC_{50} is the concentration at which 50% of the effect is observed, E_{max} is the maximum effect, and C is drug concentration. Figure 9–3 is a plot of percent of maximum response as a function of drug concentration according to Equation 9–2. It shows a linear relationship between effect and concentration at low drug concentrations. This plot is characteristic of most concentration-response curves. It applies to in vitro experiments, which

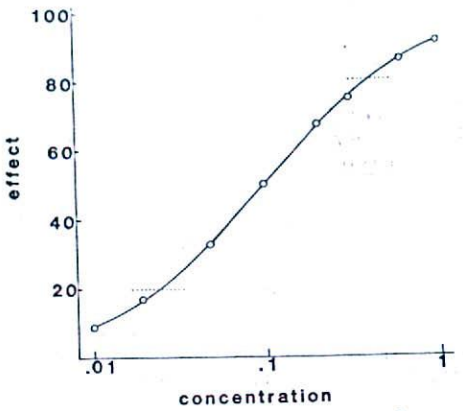

Fig. 9–4. Typical logarithmic drug concentration-effect relationship resulting from the reversible interaction of drug and receptor. Effect is expressed as percent of maximum response. The plot is approximately linear between 20% and 80% of maximum response.

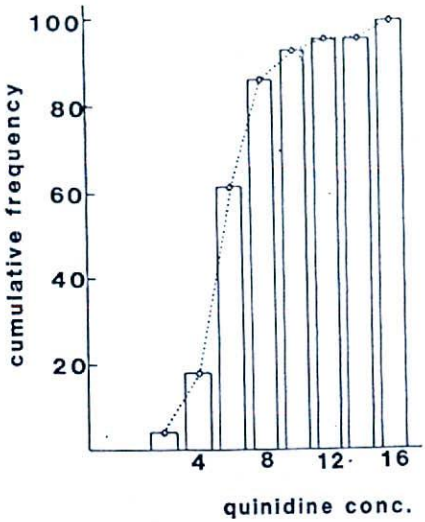

Fig. 9–5. Cumulative frequency of conversion (expressed as percent) in patients with auricular fibrillation as a function of quinidine concentration in serum (μg/ml). (Data from Sokolow, M., and Edgar, A.L.[6])

include studies of drug action on enzymes, other proteins, microorganisms, or isolated tissues or organs, to animal studies, and to clinical investigations in human patients.

A more common representation of concentration-response data is a plot of response versus the logarithm of the concentration (Fig. 9–4).[4,5] The most important feature of this transformation is the apparently linear relationship between response and drug concentration at concentrations producing effects of between 20% and 80% of the maximum effect. The logarithmic transformation of drug concentration gives rise to the following widely used, empirical relationship:

$$\text{Effect} = S \log [C] + I \qquad (9\text{–}3)$$

where S is the slope of the effect-log concentration plot and I is an empiric constant.

In some cases, the effect-concentration relationship is steeper or shallower than predicted from Eq. 9–2. A better fit may be obtained by describing the relationship as follows:

$$E = E_{max} C^n / (EC_{50}^n + C^n) \qquad (9\text{–}3a)$$

where n is a shape factor that accounts for deviations from a perfect hyperbola. If $n = 1$, Equation 9–3a is the same as Equation 9–2a and plots of effect versus drug concentration or log drug concentration will be similar to those shown in Figures 9–3 and 9–4, respectively. The larger the value of n, the steeper is the apparently linear portion of the effect-log concentration plot. Assuming that Equation 9–3 applies, the larger the value of n, the larger is the value of S. When $n = 1$, a 16-fold increase in drug concentration around the EC_{50} is needed to increase the response from 20 to 80% of maximum; when $n = 2$, only a 4-fold increase is required.

The reversible drug-receptor interaction model adequately accounts for the *graded responses* produced by many drugs; as we increase the dose or concentration, we also increase the intensity of effect. However, there are some pharmacologic or toxic responses that cannot be measured on a continuous basis. For example, an anticonvulsant drug either prevents a seizure or does not prevent a seizure. The same is true for certain effects of antiarrhythmic drugs. The arrhythmia either is or is not suppressed. Such effects are known as *quantal* or *all-or-none* responses.

In the case of all-or-none responses, the relationship between concentration and response can be developed in terms of the frequency of an event in the patient population. Figure 9–5 shows the cumulative frequency of conversions in 28 patients with auricular fibrillation as a function of serum concentrations of quinidine.[6] This frequency histogram has roughly the same shape as the effect-concentration curve shown in Figure 9–3. The data

show that serum quinidine levels of 5 to 6 μg/ml are required to get conversion in 50% of the population; serum levels of 7 to 8 μg/ml are needed for an 80% response rate.

DRUG CONCENTRATION AND THERAPEUTIC EFFECTIVENESS

Since the response to a drug increases with increasing drug concentration, it may seem reasonable to suggest that patients who do not respond to a drug should be given more drug to produce higher blood levels. This simple view of drug therapy may apply to those drugs that produce a single, specific pharmacologic effect, the so-called magic bullet, but it does not apply to most drugs. Perhaps the antibiotics come closest to this ideal. Most drugs produce multiple effects; they simultaneously affect more than one, sometimes many, organs or systems in the body. The β-blockers simultaneously affect beta-adrenergic receptors in heart and bronchi, producing desired effects on the cardiovascular system and unwanted effects, such as bronchospasm, on the pulmonary system. For this reason, a drug like propranolol should be avoided in patients with asthma or bronchitis.

The multiple effects of drugs greatly complicate the drug concentration-therapeutic effectiveness relationship. Figure 9–6 is a schematic representation of the desired pharmacologic effect, lack of effect, minor side effects, major side effects, and therapeutic effectiveness relationships with serum concentrations of procainamide in patients receiving this drug for the treatment of arrhythmias.[7,8] The desired pharmacologic effect is the suppression of abnormal cardiac rhythms. Side effects are classified as minor if the drug need not be withdrawn, and as serious when disturbances of cardiovascular function require discontinuation of the drug. Serious toxic effects include severe hypotension, atrioventricular and intraventricular conduction disturbances, appearance of major new ventricular arrhythmias, and cardiac arrest.

The frequency-drug concentration curves for desired pharmacologic effect, minor toxicity, and major toxicity shown in Figure 9–6 resemble portions of the concentration-effect curves shown in Figures 9–3 to 9–5. Arrhythmias will be suppressed in the majority of patients at procainamide concentrations of 4 μg/ml or more. Procainamide is a useful drug because drug concentrations associated with desired effect are lower than those associated with serious toxicity. Many patients, however, do not respond to procainamide until concentrations of 6 to 10 μg/ml are reached: some of these patients

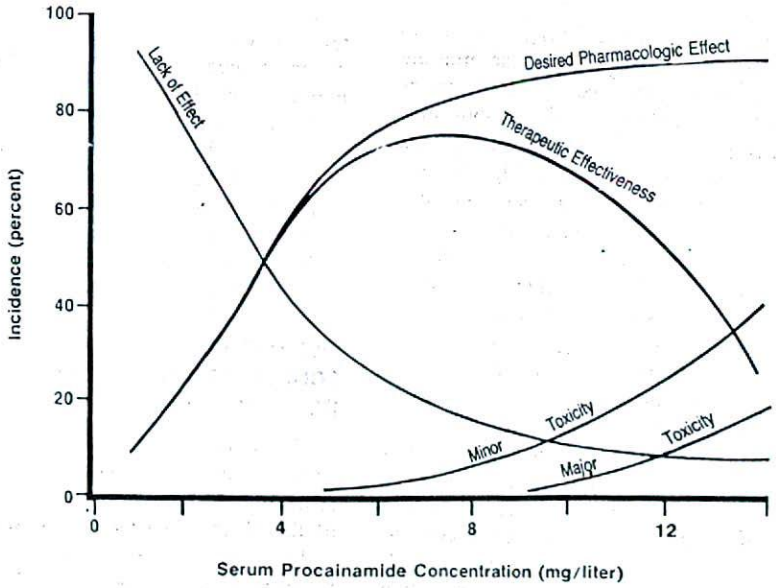

Fig. 9–6. Schematic representation of the incidence of desired pharmacologic effect (suppression of arrhythmias), lack of effect, minor and major side effects, and therapeutic effectiveness (desired pharmacologic effect minus toxicity) as a function of procainamide concentration in serum. (From Rowland, M., and Tozer, T.N.[8])

will experience minor adverse effects. Although these effects are considered minor, they may be sufficiently troubling to the patient to prompt self-discontinuation of the drug. A small number of patients do not respond to procainamide until concentrations of 10 to 14 μg/ml are achieved; many of these individuals will be plagued with minor adverse effects, and some will experience major toxicity that requires discontinuing the drug.

This description of the effects of procainamide in a patient population clearly shows that although the pharmacologic effectiveness increases with drug concentration, the therapeutic effectiveness does not. Therapeutic effectiveness may be viewed as the difference between pharmacologic effectiveness and toxicity or the benefit-to-risk ratio of a drug. Therapeutic effectiveness of procainamide increases with drug concentration to a maximum value, about 7 to 8 μg/ml, but then decreases with increasing drug concentration. These characteristics are typical of almost all drugs used today and lead us to the idea of a *therapeutic concentration range*, bounded at one end by the need to have pharmacologic effectiveness and at the other by the need to minimize toxicity.

The therapeutic concentration range of procainamide is about 4 to 10 μg/ml. Most patients do not respond to lower concentrations of the drug and some patients will experience serious adverse effects at higher concentrations. The establishment of a therapeutic concentration range for a population is hardly absolute; it requires judgment as to the importance of adverse effects. For example, if many patients elect to discontinue procainamide when faced with its minor adverse effects, it may be more realistic to define the therapeutic range as 4 to 8 μg/ml. For this reason, one may find more than one set of values cited in the literature for the therapeutic concentration range of a drug.

The therapeutic concentration range applies to an individual patient only to the extent that this patient is typical of the population. Figure 9–6 shows that some patients will benefit from serum concentrations of procainamide as low as 1 to 2 μg/ml, whereas other patients can tolerate concentrations as high as 12 to 14 μg/ml. It is helpful, therefore, to think of a therapeutic concentration range only as a guide for optimizing drug therapy.

Therapeutic concentration ranges have now been developed for perhaps 20 to 30 drugs; some are listed in Table 9–1. Experience has shown that the range for most of these drugs is narrow; the ratio of the upper limit to the lower limit is often only 2 or 3. The significance of the upper limit may be different for different drugs. Most often the upper limit reflects toxicity. However, in the case of nortriptyline, and perhaps other antidepressants, the upper limit reflects loss of effectiveness without signs of increasing toxicity. When toxicity is limiting it may be an extension of the pharmacologic effect of the drug (e.g., the bleeding problem associated with high concentrations of warfarin) or a different effect seemingly unrelated to the desired effect of the drug (e.g., the seizures resulting from high concentrations of theophylline). In some situations a drug may be used for more than one indication and different therapeutic ranges may apply to different conditions. The value cited in Table 9–1 for salicylic acid applies to its use as an anti-inflammatory agent in rheumatoid arthritis. Lower concentrations are adequate when the drug is used as an analgesic for simple aches and pains; but higher concentrations of salicylate may be needed for the treatment of rheumatic fever.

Table 9–1. Usual Therapeutic Concentration Range for Specific Drugs

Drug	Disease	Therapeutic range
Carbamazepine	Epilepsy	4–12 μg/ml
Digoxin	Congestive heart failure	0.5–2.0 ng/ml
Disopyramide	Arrhythmias	3–5 μg/ml
Gentamicin	Infection	1–10 μg/ml
Lidocaine	Arrhythmias	2–6 μg/ml
Nortriptyline	Depression	50–150 ng/ml
Phenytoin	Epilepsy	10–20 μg/ml
Procainamide	Arrhythmias	4–8 μg/ml
Salicylic acid	Rheumatoid arthritis	10–30 mg/dl
Theophylline	Asthma	10–20 μg/ml

FACTORS COMPLICATING CONCENTRATION-RESPONSE RELATIONSHIPS

Most drugs are found in the blood in both free and bound forms. Drugs commonly bind to plasma proteins and, sometimes, to the formed elements of the blood. The degree of binding may vary widely from one patient to another. Only free drug is able to diffuse from the blood to the extravascular site of drug action. It would seem reasonable that concentration-response relationships be based on free rather than total drug concentration in blood or plasma, but usually this is not the case. All values cited in Table 9–1 refer to total drug con-

centrations. The determination of free drug concentration presents serious technical problems. Although progress is being made, routine measurement of free drug is still some time off.

When variability in plasma protein binding of a drug is considerable, difficulty in estimating free drug concentration is a complicating factor to establishing a concentration-response relationship for a population. The therapeutic concentration range of 10 to 20 μg/ml for phenytoin, in the treatment of epilepsy, is appropriate for patients with normal renal function, but it may be as low as 5 to 10 μg/ml for patients with uremia because plasma protein binding of phenytoin is substantially reduced in these patients.

The therapeutic range for phenytoin in terms of free drug concentration is about 1 to 2 μg/ml. On the average, phenytoin is bound to plasma proteins to the extent of about 90%. Reduced binding occurs in patients with impaired renal function, but the free drug concentration needed to produce optimal effects in most patients is still 1 to 2 μg/ml.

Some drugs have active metabolites that contribute to the pharmacologic effects and therapeutic effectiveness of the drug; examples include imipramine, propranolol, phenacetin, diazepam, procainamide, and meperidine. Concentration-response relationships based on the concentration of parent drug alone may be misleading. Efforts to establish a therapeutic concentration range for amitriptyline, an antidepressant drug, take into account the concentration of both amitriptyline and its active metabolite, nortriptyline.

Drugs that are subject to presystemic metabolism may result in higher concentrations of active metabolites after oral administration than after intravenous administration. Under these conditions, concentration-effect curves based only on the concentration of administered drug may be different for oral and intravenous doses. Figure 9–7 shows concentration-effect curves for propranolol. The drug appears to be much more active after oral than after intravenous administration. This anomalous result can be explained by the formation of significant amounts of an active metabolite, 4-hydroxypropranolol, when propranolol is given orally.[9] Presystemic formation of active metabolites also seems to explain why the change in electrocardiograph QT interval per mg/L quinidine concentration is greater after oral dosing than after intravenous administration.[10]

Many drugs are administered as racemates,

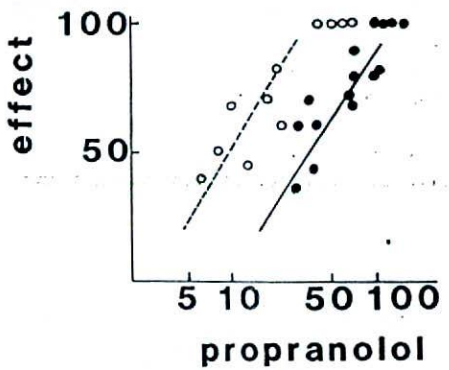

Fig. 9–7. Relationship between effect (percent block of exercise-induced tachycardia) and propranolol concentration (ng/ml) in plasma (log scale) after oral (○) and intravenous (●) administration. (Data from Coltart, D.J., and Shand, D.G.[9])

mixtures of two optically active enantiomorphs of the drug. In some cases there are considerable differences between the enantiomorphs in terms of pharmacologic activity and rates of elimination. Attempts to establish concentration-effect relationships based on total drug concentration can lead to confusing and erroneous results. Ideally, the concentration-response relationship for each enantiomorph, administered separately, should be established before attempting to resolve the effects of the racemate.

Delays in response are sometimes encountered after administering a drug. Figure 9–8 shows plasma concentrations of cocaine after rapid intravenous injection and its effect on heart rate in adult

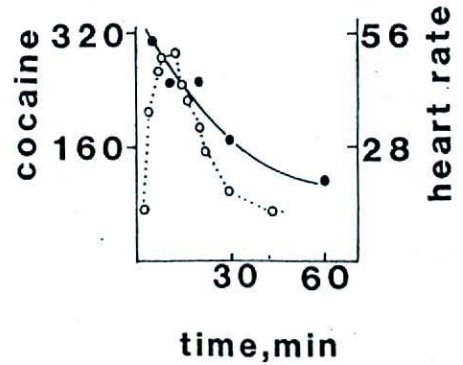

Fig. 9–8. Relationship between cocaine concentrations in plasma (●) (ng/ml) and the percent change in heart rate (○) after a 32-mg intravenous dose. (Data from Javaid, J.I., et al.[11])

cocaine users.[11] Cocaine concentrations are at a maximum almost immediately after injection, but the maximum effect of the drug is delayed 10 to 12 min. These delays usually reflect the time needed for equilibration of drug between the blood and the site of effect. They are often short, only minutes, but may be longer when the drug diffuses slowly into the site. For example, the maximum cardiac effects of digoxin are not seen for an hour or more after rapid intravenous injection of the drug.

Long delays may also be encountered when the clinical response is an indirect measure of drug effect. Warfarin and other coumarin anticoagulants directly inhibit the synthesis of certain clotting factors. The anticoagulant effect of warfarin is an indirect result of the inhibition and ultimate depletion of body stores of these clotting factors; depletion is a relatively slow process. Accordingly, the maximum effect of warfarin on blood clotting is not seen until 1 or 2 days after a rapidly absorbed oral dose of the drug. A dissociation between the direct effects of a drug and its clinical manifestations may also explain why up to 4 to 6 weeks of tricyclic antidepressant therapy may be required before maximum benefits are observed.

The effectiveness of a drug can diminish with continual use. This situation is often called an acquired tolerance to the effects of a drug. Several kinds of acquired tolerances have been described, including pharmacokinetic and pharmacodynamic tolerances. The rate of metabolism of some drugs (e.g., carbamazepine) increases with repeated administration so that a maintenance dose produces lower blood levels than those following the initial dose. This is an example of pharmacokinetic tolerance; it can usually be overcome by increasing the dose of the drug. Pharmacodynamic tolerance means that the same concentration of drug in the blood will elicit a diminished pharmacologic response after a period of drug use than after initial treatment. Animals made tolerant to barbiturates or alcohol show significantly less sedation and ataxia than do nontolerant animals at the same blood concentrations.

Tolerance to the hemodynamic effects of nitroglycerin and other organic nitrates is a serious clinical problem. The problem is most evident with transdermal nitroglycerin patches, sustained release forms of isosorbide dinitrate, and continuous intravenous infusions of nitroglycerin. In each case, relatively high and continuous plasma levels of nitrates are maintained, while the effects of the drug fade away. Intermittent application of nitroglycerin ointment or oral administration of conventional tablets or capsules of isosorbide dinitrate 2 or 3 times a day has not been found to produce tolerance, presumably because nitrate levels go up and down and there are periods when nitrate levels in plasma are negligible.

Packer et al.[12] treated patients with severe chronic heart failure with iv nitroglycerin given continuously over 48 hr. Twenty-four hr before nitroglycerin, each patient received a 40-mg oral dose of isosorbide dinitrate. A second and third dose of isosorbide dinitrate were given 2 hr and 24 hr after stopping the nitroglycerin infusion.

Within 2 hours of starting nitroglycerin, significant hemodynamic benefits were observed in all patients: an increase in stroke volume index and falls in mean arterial pressure and systolic vascular resistance. These initial responses, however, were markedly attenuated after 48 hr of uninterrupted treatment. Seventeen of the 24 patients had a complete loss of hemodynamic effects, and effects were significantly diminished in the others.

All patients responded to the first dose of isosorbide dinitrate but showed no response to the second dose, given 2 hr after the nitroglycerin infusion. Responsiveness was restored when isosorbide dinitrate was administered 24 hr after discontinuing the infusion. This study demonstrated that acute tolerance to nitroglycerin develops within hours of starting a constant rate iv infusion and that this treatment also gives rise to cross-tolerance to the effects of isosorbide dinitrate and probably other organic nitrates.

The acute tolerance to nitroglycerin has prompted prescribers to recommend that nitroglycerin patches be applied for only 12 to 16 hr a day (with a new patch applied every morning), rather than continuously as currently recommended by the manufacturers. Studies have determined that a 8 to 12 hr drug-free period is sufficient to overcome nitrate tolerance and restore responsiveness.

Cowan et al.[13] compared continuous and intermittent treatment with a nitroglycerin patch delivering 10 mg every 24 hr in patients with stable exertional angina. Patches were changed twice daily at 8 AM and 8 PM. In the continuous treatment arm of the study both patches were active; during intermittent treatment only the morning patch was active. On the eighth day, exercise testing was carried out at 8:30 AM with the previous evening's

patch in place. A new (active) patch was applied at 9 AM and the patients were retested at 12:30 PM.

The first exercise test on the eighth day found no difference between those wearing an active patch (continuous group) and those wearing a placebo patch (intermittent group). Three and a half hr after application of an active patch, there was a marked improvement in exercise time for the intermittent group but no effect in the continuous group. The investigators concluded that attempts at 24-hr protection with nitrates in angina may be self-defeating.

The mechanism for the acute tolerance to organic nitrates is not completely understood. One theory suggests that nitrates increase coronary blood flow by interacting with sulfhydryl groups in vascular smooth muscle, leading to the production of S-nitrosothiols. These compounds activate guanylate cyclase and increase the intracellular concentration of cyclic guanosine monophosphate (cyclic GMP), resulting in vascular relaxation and vasodilation. Tolerance may develop if sulfhydryl availability is limited, perhaps because continuous exposure to nitrates used them up. If this hypothesis is correct, an exogenous source of sulfhydryl groups, such as N-acetylcysteine, might reverse tolerance.

To test the sulfhydryl hypothesis, Packer et al.[12] administered oral N-acetylcysteine to patients during prolonged nitroglycerin infusion. The patients were initially responsive to nitroglycerin but at the time N-acetylcysteine was given they were completely tolerant. In these patients, N-acetylcysteine produced a significant improvement in all hemodynamic variables, a response almost as strong as the initial response to nitroglycerin, but had no hemodynamic effects in patients with heart failure who were not receiving nitroglycerin.

Tolerance to the acute effects of nicotine has also been observed. When a short (10-min) intravenous infusion of nicotine is given every half hr, the increase in heart rate produced by the first infusion is greater than that produced by any of the following infusions, despite the fact that with each successive infusion higher blood levels of nicotine occur until steady state is reached.[14] Also, the increase in heart rate after iv nicotine is much smaller when the injection is given after subjects had smoked several cigarettes than after overnight abstinence from smoking.[15]

TIME COURSE OF DRUG EFFECTS

A drug that produces an all-or-none response is effective as long as its concentration remains above some minimum concentration at the site of action. Therefore, the duration of effect is a function of dose and the rate of removal from the site of action. The larger the dose and the slower the rate of removal, the longer is the duration of action. Two factors can control the rate of removal of drug from the site of action: redistribution of drug from the site to other, less well-perfused tissues, or elimination of drug from the body. The short-lived effect of thiopental on the central nervous system is an example of redistribution-controlled removal rather than elimination-controlled removal from the site of action. In most cases, however, the rate of removal of drug from the site of action probably corresponds to its rate of removal from the body.

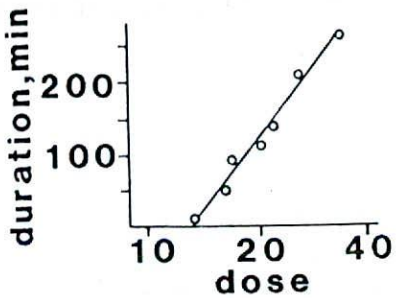

Fig. 9–9. Relationship between intravenous dose of pentobarbital (mg/kg, log scale) and duration of anesthesia in monkeys. (Data from Levy, G.[16])

After a bolus intravenous dose of a drug that distributes rapidly, the amount of drug in the body (A) is given by:

$$\log A = \log \text{Dose} - kt/2.303 \qquad (9\text{–}4)$$

where k is the first-order elimination rate constant. Body levels decline until a level is reached that we shall define as the minimum effective level of drug in the body (A_{min}). At this time, $t = t_d$, the duration of effect of the drug. It follows that:

$$\log A_{min} = \log \text{Dose} - kt_d/2.303 \qquad (9\text{–}5)$$

Solving Equation 9–5 for the duration of effect (t_d) yields:

$$t_d = 2.303(\log \text{Dose} - \log A_{min})/k \qquad (9\text{–}6)$$

Equation 9–6 indicates that under these conditions a plot of duration of effect versus log dose yields a straight line with a slope equal to 2.303/k and an intercept, on the x-axis, corresponding to A_{min} (Fig. 9–9).[16] When multiple doses of a drug are administered, the duration of effect may in-

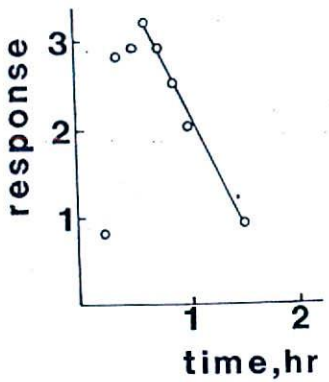

Fig. 9–10. Time course of euphoric response after an oral dose of cocaine. (Data from Mayersohn, M., and Perrier, D.[17])

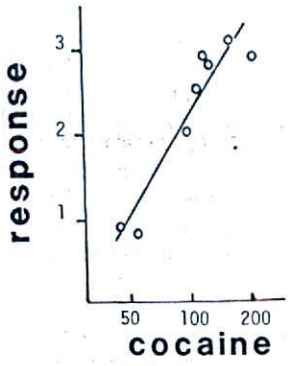

Fig. 9–11. Logarithmic cocaine concentration in plasma (ng/ml)-response relationship. (Data from Mayersohn, M., and Perrier, D.[17])

crease with each dose until steady state is reached because the initial amount of drug in the body following a dose will be higher than that of the preceding dose.

In principle, the duration of effect of a drug may be controlled by the dose. Evaluation of Equation 9–6 shows that the duration of effect increases by one half-life (0.693/k) with each doubling of the dose.[8] In practice, however, duration of effect is largely a function of the therapeutic index and half-life of the drug. The ratio of Dose to A_{min} cannot exceed the therapeutic index of the drug. If this ratio is small, on the order of two, the drug must be given no less frequently than once every half-life to avoid adverse effects.

A more useful relationship for drugs that produce graded responses is one that correlates the intensity of effect with the time after administration. We know that drug concentration declines in an exponential manner with time after administration; but to relate concentration, response, and time, we need to select a concentration-response relationship. The log concentration-effect relationship (Eq. 9–3) is a particularly useful one. Since,

$$\log C = \log C_o - kt/2.303 \qquad (9–7)$$

and

$$\text{Effect} = S \log C + I \qquad (9–8)$$

where C is drug concentration in blood or plasma, S is an effect parameter relating the change in effect to the change in log C, and I is an empirical constant, it follows that:

$$\text{Effect} = (S \log C_o + I) - Skt/2.303 \qquad (9–9)$$

or

$$\text{Effect} = E_o - Skt/2.303 \qquad (9–10)$$

Equation 9–10 indicates that the intensity of effect of a rapidly distributed drug will decline at a constant (zero-order) rate after an intravenous bolus dose. The slope of the linear plot of effect versus time is equal to $-Sk/2.303$.

Figure 9–10 shows a plot of the intensity of euphoria after an oral dose of cocaine.[17] The effect of the drug increases with time, reaches a maximum about 60 to 90 min after administration, and thereafter declines in a linear manner, in accordance with Equation 9–10. The slope of the line ($-Sk/2.303$) is equal to -0.0221 effect units/min. A plot of effect versus log concentration of cocaine, shown in Figure 9–11, is also linear; the slope (S) of this plot is equal to 3.9 effect units. From these data we may calculate that $Sk = 0.051$ effect units/min, $k = 0.0131$ min^{-1}, and $t_{1/2} = 53$ min. This estimate of the half-life of cocaine, determined solely from effect data, agrees with the value of 57 min determined from a semilogarithmic plot of cocaine concentration versus time.

Cocchetto has applied these relationships to the constant rate intravenous infusion of short-acting drugs.[18] At steady state, the following equation applies:

$$E_{ss} = S \log K_o - (S \log Cl + I) \qquad (9–11)$$

where E_{ss} is the effect at steady state, k_o is the zero-order infusion rate, and Cl is the clearance of the drug. Figure 9–12 shows that the steady-state mean arterial blood pressure in a patient with malignant

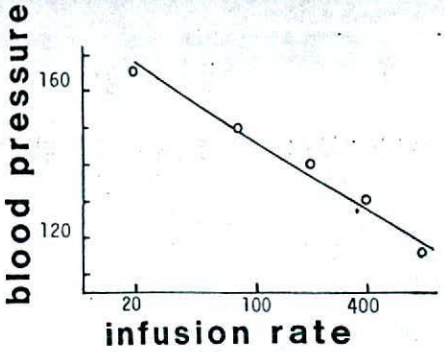

Fig. 9–12. Relationship between steady-state mean arterial blood pressure (mm Hg) and sodium nitroprusside infusion rate (μg/min, log scale). (Data from Cocchetto, D.M.[18])

hypertension is a linear function of the log of infusion rate of nitroprusside, in accordance with Equation 9–11. Based on these data and on the postinfusion rate of decline of effects, the half-life of nitroprusside was calculated to be 16 min, a value consistent with the fleeting effects of the drug when it is given as an intravenous bolus dose.

The time course of drug effects following rapid intravenous injection of a drug may be far more complicated than that suggested by Equation 9–10, because the log concentration-effect relationship applies only to a limited range of drug concentrations (i.e., those concentrations producing effects between 20% and 80% of the maximum effect). An excellent example of these complexities has been provided by Rowland and Tozer.[8]

Figure 9–13 shows the time course of effect following rapid intravenous injection of a drug. The dose is sufficiently large to yield concentrations that elicit a maximum response. The log concentration-response plot is shown in the inset. Segmenting the plots into three regions, 0 to 20% maximum response, 20 to 80% maximum, and 80 to 100% maximum, is a convenient way to describe the complex time course of effect.

The initial drug concentration produces a maximum effect. Drug concentration falls rapidly over the first hour (50% decrease) but response remains nearly constant at about 90 to 100% of maximum (region 3). Only after 2 hr, when concentration falls below 3 ng/ml and response falls below 80% maximum, does response begin to decline more

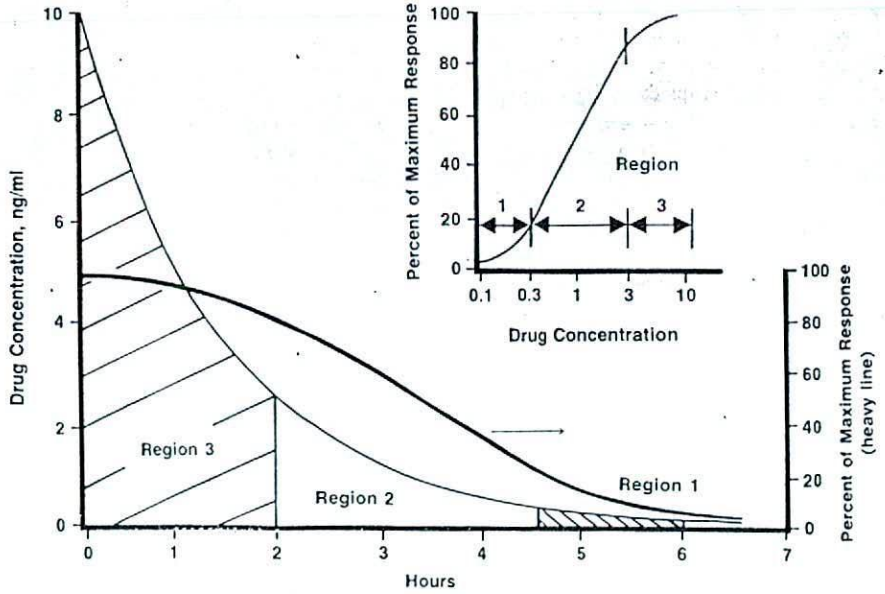

Fig. 9–13. The decline in the intensity of pharmacologic effect with time, following a single large dose, has 3 distinct parts corresponding to the regions of the concentration-response curve. There is little change in effect in region 3 despite a large change in drug concentration; effect declines linearly in region 2 and exponentially in region 1. (From Rowland, M., and Tozer, T.N.[8])

rapidly (region 2). In region 2 the drug concentration-response relationship is described by Equation 9–3, and response declines at a constant rate of about 20%/hr according to Equation 9–10. When the concentration falls below 0.3 ng/ml (region 1), the fall in response is exponential and parallels the fall in concentration.

As previously discussed, the usual response to many drugs falls in region 2; effect is lost at a constant rate. There are some reports showing an exponential loss of drug effect with time, suggesting that response to these drugs lies in region 3. The usual doses of β-blockers produce responses that appear to fall into region 1; effects on blood pressure and heart rate are relatively constant over large concentration ranges.

By focusing on drug concentration, we have learned a great deal about drug effects. In the following chapters, you will find that much is also known about the factors that influence drug concentration (pharmacokinetic variability). This information has stimulated progress in the area of individualized and optimized drug treatment. The final step, an understanding of pharmacodynamic variability, remains elusive, because it is difficult to study. Here too, however, progress is being made. We are beginning to learn that age, genetics, and diseases can alter the receptor's sensitivity to a drug. We are at the threshold of seminal advances in drug discovery, and it is vitally important that the individual patient reaps the full benefits of this windfall.

REFERENCES

1. Smith, S.E., and Rawlins, M.D.: Variability in Human Drug Response. London, Buttersworth, 1973, pp. 1–2.
2. Kato, R., Takanaka, A., and Onoda, K.: Individual difference in the effect of drugs in relation to the tissue concentration of drugs. Jpn. J. Pharmacol., *19*:260, 1969.
3. Schnell, R.C., et al.: Similarity in CNS sensitivity to hexobarbital in the rat and mouse as determined by an analytical, a pharmacokinetic, and an electroencephalographic measure. Pharmacology, *13*:20, 1975.
4. Winkle, R.A., et al.: Clinical efficacy and pharmacokinetics of a new orally effective antiarrhythmic tocainide. Circulation, *54*:884, 1976.
5. Holford, N.H.G., and Sheiner, L.B.: Understanding the dose effect relationship: clinical application of pharmacokinetic-pharmacodynamic models. Clin. Pharmacokinet., *6*:429, 1981.
6. Sokolow, M., and Edgar, A.L.: Blood quinidine concentration as a guide in the treatment of cardiac arrhythmias. Circulation, *1*:576, 1950.
7. Koch-Weser, J.: In Pharmacology and the Future: Problems in Therapy. Vol. III. Edited by G.T. Okita and G.H. Acheson. Basel, Karger, 1973, pp. 69–85.
8. Rowland, M., and Tozer, T.N.: Clinical Pharmacokinetics: Concepts and Applications. 2nd Ed. Philadelphia, Lea & Febiger, 1989.
9. Coltart, D.J., and Shand, D.G.: Plasma propranolol levels in the quantitative assessment of β-adrenergic blockade in man. Br. Med. J., *3*:731, 1970.
10. Holford, N.H.G., et al.: The effect of quinidine and its metabolites on the electrocardiogram and systolic time intervals: Concentration-effect relationships. Br. J. Clin. Pharmacol., *11*:187, 1981.
11. Javaid, J.I., et al.: Cocaine plasma concentrations: Relation to physiological and subjective effects in humans. Science, *202*:227, 1978.
12. Packer, M., et al.: Prevention and reversal of nitrate tolerance in patients with congestive heart failure. N. Engl. J. Med., *317*:799. 1987.
13. Cowan, C., et al.: Tolerance to glyceryl trinitrate patches: prevention by intermittent dosing. Br. Med. J., *294*:544, 1987.
14. Rosenberg, J., Benowitz, N.L., Wilson, M.: Disposition kinetics and effects of intravenous nicotine. Clin. Pharmacol. Ther., *28*:517. 1980.
15. Russell, M.A.H., Feyerabend, C.: Cigarette smoking. A dependence on high nicotine boli. Drug Metabolism Revs., *8*:29, 1978.
16. Levy, G.: Kinetics of pharmacologic effects. Clin. Pharmacol. Ther., *7*:362, 1966.
17. Mayersohn, M., and Perrier, D.: Kinetics of pharmacologic response to cocaine. Res. Comm. Chem. Pathol. Pharmacol., *22*:465, 1970.
18. Cocchetto, D.M.: Kinetics of pharmacological effects on constant-rate intravenous infusion. J. Pharm. Sci., *70*:578, 1981.